REMARKS

Applicant respectfully requests reconsideration. Claims 28-34 and 36 were previously pending in this application. Withdrawn claims 30 and 34 have been canceled. Claims 28 and 29 are amended herein. As a result, claims 28-29, 31-33 and 36 are still pending for examination with claims 28 and 29 being independent claims. The amendment and cancellation of claims are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and canceled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and or divisional application(s). No new matter has been added.

Rejection Under 35 U.S.C. 103

Claims 28-29, 31-33 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kataoka et al. 1992 Jpn. J. Cancer Res. Vol. 83 pgs. 244-247 in view of Goodchild et al. 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al., U.S. Patent 5,723,335 March 3, 1009 (filed March 25, 1994), and Cheng et al., U.S. Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994).

Although Applicant disagrees with the rejection of record, the claims have been narrowed to encompass an oligonucleotide having the sequence 5' AACGTT 3' solely in order to advance prosecution. The Examiner has cited Kataoka et al for disclosing an ODN having the sequence 5'TGACGTC 3'. The Examiner has not indicated that Kataoka et al discloses the sequence 5' AACGTT 3'. Applicant does not see in Kataoka et al any disclosure of an ODN having the sequence 5' AACGTT 3'. The combination of references including Kataoka et al does not result in the invention as claimed. Thus, in view of the amendments to the claims, it is requested that the rejection be withdrawn.

Claims 28-29, 31-33 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kuramoto et al. 1992 Jpn J. Cancer Res Vol. 83 pgs. 1128-1131 in view of Goodchild et al., 1990 The American Chemical Society, Vol. 1, No. 3 pgs 165-182, Hutcherson et al. U.S. Patent 5,723,335 March 3, 1998 (filed March 25, 1994).

Applicant previously argued that the skilled artisan would not have modified the ODN of Kuramoto et al by adding phosphorothioate internucleotide linkages because of the unpredictability of phosphorothioate linkages. The Examiner has dismissed Applicant's arguments and asserted that it was known in the art that phosphorothioate backbones should be used with immunostimulatory oligonucleotides and that a change in backbone would affect the properties of the immunostimulatory oligonucleotides. In the Advisory Action the Office continues to assert that the skilled artisan would have known to use modified oligonucleotides because of the teachings found in Agrawal et al and Hutcherson et al. Applicants respond to each of the points raised in the discussion below. However, it is first noted that the references previously cited by Applicant have not been addressed. It is requested that these be addressed. Further, it is believed that Applicant's arguments were dismissed as attorney argument. In support of Applicant's arguments a Declaration of Dr. Cy Stein is enclosed herewith.

Dr. Stein was an expert in the field of phosphorothioate modifications at the time of the invention. As shown in paragraph 7 of the attached declaration Dr Stein has studied oligonucleotide backbone modifications for more than 17 years. In response to a very similar argument on the basis of 35 USC 103 in Patent Interference 105171, Dr. Stein presented evidence of the unpredictability of phosphorothioate backbone modifications at the time of the invention. Interference 105171 was an Interference involving US Patent 6,207,646 by Krieg et al. The instant application is a continuation of US 6,194,388. US 6,207,646 also derives priority from US 6,194,388. Dr. Stein is not a co-inventor of the instant patent application. However, Dr. Stein was compensated for the preparation of his declaration in Patent Interference 105171.

The rejection addressed by Dr. Stein in the attached Declaration related to whether it would have been obvious to the skilled artisan in the 1994-1996 time frame to modify the ODN of Kataoka et al by adding phosphorothioate internucleotide linkages. The issue is addressed in paragraphs 10-28 of the Declaration of Dr. Stein. Dr. Stein explains why the skilled artisan in the 1994-1996 time

frame would not have known the impact of adding phosphorothioate internucleotide linkages on the immunostimulatory activity described in Kataoka et al, which is similar to the disclosure of Kuramoto et al.

In summary, it is taught in the attached declaration of Dr. Stein that

> Those of ordinary skill in the art did not know the mechanisms through which the nucleic acids of Katoaka or Sato achieved immune stimulation. Without knowledge of the mechanisms through which these nucleic acids achieved immune stimulation, it would have been completely unpredictable to one of ordinary skill in the art whether a phosphate backbone modification would totally destroy the immunostimulatory capability of the Kataoka or Sato nucleic acids.
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> Phosphate backbone modifications were, and still are, known to have unpredictable and undesirable effects on nucleic acids. Among the complications introduced by phosphorothioate modification is the creation of stereochemistry. The sulfur in a phosphorothioate modification introduces stereochemistry at each bond where it is present, creating distinct versions of the molecule. The two stereochemical forms of the phosphorothioate linkage each produce molecules with biological activities that can be distinct from each other, and distinct from an unmodified nucleic acid, having the same base pairs. Because stereochemistry is introduced at each site with a phosphorothioate bond, a molecule with several or many such bonds is actually an enormously complex mixture of different chemical entities with unpredictable properties. One of skill in the art would not have known whether the introduction of stereochemistry would affect immunostimulation. In addition to the stereochemistry, the sulfur atom can have further effects on the activity of the nucleic acid simply due to its being much larger than the oxygen.
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> In fact, phosphorothioate can unpredictably redirect oligonucleotide activity to create biological activity against targets where there previously was none. One of ordinary skill in the art would have known that binding targets and binding capabilities could impact immunostimulatory capabilities of a nucleic acid. In the absence of Dr. Krieg's work, it would not have been known from 1994 through 1996 whether a phosphorothioate bond or phosphorodithioate would substantially change or redirect the binding of an oligonucleotide necessary for immunostimulation.
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> In Kataoka, there were palindromes that were inactive, therefore, even though Kataoka attributed the "activity" of the oligonucleotides to palindromes, it would have been unclear to one of ordinary skill in the art what characteristics of the molecule were actually critical for activity. In the absence of Dr. Krieg's work as shown in the '646 patent and the 1995 *Nature* paper, from 1994 through 1996, it would not have been predictable that a phosphate backbone modification to a molecule shown to be "active" in Kataoka would allow the molecule to retain its immune stimulatory effects.

In the Declaration, Dr. Stein provides examples in support of the above statements. It is requested that the Patent Office consider the evidence provided by Dr. Stein particularly in paragraphs 10-28 of the attached Declaration.

The skilled artisan at the time of the invention would not have combined the teachings of Kuramoto et al with Goodchild, Agrawal or Hutcherson to produce a phosphorothioate modified ODN because of the unpredictability of phosphorothioate backbone modifications. At the time of the invention it was unknown whether phosphorothioate backbones should be used with immunostimulatory oligonucleotides. It was not clear how a change in backbone would affect the properties of phosphodiester based immunostimulatory oligonucleotides. The Declaration of Dr. Stein provides evidence of this unpredictability. It is only in hindsight, using Applicant's disclosure, that the skilled artisan have been motivated to make such a combination.

The Office has cited Agrawal and Hutcherson as support that the skilled artisan would have used phosphorothioate linkages in immunostimulatory ODN. It is stated in the Advisory Action (pages 9-10) that Agrawal teaches that phosphorothioate backbones "should be used with immunostimulatory oligonucleotides". Applicant is not aware of such a teaching in Agrawal et al. Agrawal et al (US Patent No. 5194428) describes antisense ODN for treating influenza virus infection. In particular it is taught that the antisense ODN "have antiviral activity against influenza virus as a result of their ability to hybridize to a selected region of influenza virus RNA and inhibit its ability to serve as a template for synthesis of encoded products". (Abstract). Antisense is a different mechanism of action than immune stimulation. Agrawal does not provide a teaching to the skilled artisan that phosphorothioate backbones should be added to immunostimulatory ODN.

Further it is stated that Agrawal et al "teach compositions having antiviral activity against influenza virus, which include the oligonucleotides of the present invention." Applicant is not aware of such a teaching in Agrawal et al. None of the ODN described in Agrawal et al include a 5'AACGTT 3'. In fact only one ODN shown in Agrawal et al actually has a CG dinucleotide and that is control ODN #9. In control ODN # 9 the CG is in the 5' position, such that it is not flanked on the 5' end by two nucleotides, as required by Applicant's claims.

Agrawal et al does not teach the skilled artisan that phosphorothioate modifications cause immune stimulation. The skilled artisan would not recognize any teaching in Agrawal et al that

would suggest that the ODN of Kuramoto et al could be modified and still retain the immune stimulatory activity.

It is further stated in the Advisory Action that Hutcherson et al teach that phosphorothioate ODN analogs enhance immune stimulation. However, the skilled artisan would not have modified the ODN of Kuramoto et al to add phosphorothioate linkages based on the teachings of Hutcherson because the teachings of the two references are inconsistent and further in view of the known unpredictability of the phosphorothioates in the art, as discussed above. Kuramoto et al teach that the immunostimulatory DNA is sequence specific and is representative of immunostimulatory bacterial DNA. Bacterial DNA is not phosphorothioate modified. Kuramoto et al further teach that the immunostimulatory activity of the ODN is due to the hexameric palindrome within the sequence. Hutcherson describes generally that phosphorothioate ODN analogs can provoke an immune stimulatory response. However, Hutcherson does not provide any teaching regarding inclusion of a palindrome. In fact, Hutcherson et al. teaches that it is the phosphorothioate internucleotide linkage that has immunostimulatory activity. The skilled artisan attempting to create a synthetic version of bacterial DNA that was immunostimulatory would not have been motivated to phosphorothioate modify it because of the teachings of Hutcherson. Hutcherson is describing molecules that are distinct from Kuramoto et al in that they are phosphorothioate modified and are sequence independent.

Thus, in view of the different teachings between Kuramoto et al and Hutcherson et al and the expected different mechanisms of action as well as the unpredictability of phosphorothioate bonds the skilled artisan would not have combined the teachings in the absence of hindsight.

Double Patenting Rejection

Claims 28 and 36 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 101, 107-109, 120-122 and 124 of co-pending Application No. 10/314,578. Applicants arguments have been dismissed because according to the Examiner co-pending Application No. 10/314,578 (which has now issued as US 7271156) shares a common inventor with the present application. Applicant disagrees.

Although Applicant disagrees with the rejection of record, the claims have been narrowed to encompass a specific core oligonucleotide sequence solely in order to advance prosecution. The claims are now limited to oligonucleotides including the sequence 5'-AACGTT-3'. The claims of US 7271156 are limited to ODN of SEQ ID NO 343: 5' TCGTCGTTTTGACGTTTTGTCGTT 3'. The ODN of SEQ ID NO 343 does not include a 5'-AACGTT-3' motif. Thus, none of the issued claims of US 7271156 fall within the scope of claims 28-29, 31-33 and 36 or provide a teaching suggesting the ODN of claims 28-29, 31-33 and 36. It is requested that the double patenting rejection be withdrawn.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70083US07.

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Respectfully submitted,

By _____

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